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Long term treatment of polymyalgia rheumatica with deflazacort

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Abstract

***Objectives*—To evaluate the long term efficacy and tolerability of deflazacort, a corticosteroid reputed to have only minor side effects, in the treatment of polymyalgia rheumatica (PMR).**

***Methods*—In a prospective open study, deflazacort was administered at an average initial dose of 21·8 mg/day for a mean period of 19 months in 40 patients with PMR.**

***Results*—A highly significant improvement of clinical and laboratory parameters occurred one month after therapy onset. This improvement persisted for the whole study period. Laboratory parameters of tolerability did not change during the study. Mild to moderate steroid-related side effects occurred in 57·9% of the patients**

***Conclusions*—Deflazacort is effective in the treatment of PMR. Its long term safety profile may be superior to that of other corticosteroids.**

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Polymyalgia rheumatica (PMR) is a disease of the elderly that causes pain and stiffness of the limb girdles, fever, weight loss, and an elevation of non-specific indicators of inflammation.[1] Corticosteroids are its treatment of choice. They control the symptoms of most patients and may prevent serious ocular complications when giant cell arteritis is associated. However, prolonged use of corticosteroids can result in multiple side effects.

The efficacy and tolerability of deflazacort, a derivative of prednisone,[2] was evaluated in PMR. Deflazacort is generally associated with milder bone damage than other corticosteroids[3] and with minor effects on glucose metabolism.[4]

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Patients and methods

We studied 40 consecutive outpatients with active PMR diagnosed according to Jones and Hazleman.[5] Only patients older than 50 years with an erythrocyte sedimentation rate (ESR) greater than 40 mm/hour were included.[6] They had not received steroids and gave their informed consent.

Deflazacort was administered at a mean starting dose of 21·8 mg/day with a range of 6–60 mg depending on severity of disease. The most common starting doses were 15 mg/day (15 patients, 37·5%), 30 mg/day (14 patients, 35%), and 6 mg/day (four patients, 10%). The highest dose (60 mg) was used in two patients with concomitant giant cell arteritis. Patients were evaluated monthly for one year and every six months thereafter. Deflazacort was tapered by about 20% if the patient was asymptomatic and ESR was reduced. Side effects were searched with a questionnaire and by physical examination.

In PMR recurrences (defined as signs or symptoms of PMR and/or giant cell arteritis requiring higher doses of steroids), deflazacort was increased to the latest level that had kept the patient asymptomatic. A relapse was defined as signs or symptoms of PMR requiring corticosteroid therapy after its discontinuation.

Statistics included one-way ANOVA, Student's *t* test, chi-square test with Yates' correction and the Kaplan-Meier method for survival curves. All the tests were two-tailed. The 'post-hoc comparison' was evaluated by the least significant difference method.

Results

PATIENTS

The mean age of the 40 patients (24 women/16 men) was 70·7 years (range 50–91 years). Patients were referred 4·6 months after the onset of PMR on average (range 1–14 months).

Twenty seven patients were allowed to continue treatment with NSAIDs at low doses. Of these, 15 received NSAIDs for less than three months and 12 for 9·7 months in average. The dose of NSAIDs in these 12 patients was constant throughout the study.

FOLLOW UP

Two patients were lost to follow up on the first and third month. In the remaining 38 patients, the treatment lasted a mean of 18·9 months (range 9–48 months). Of the 23 patients with remission, seven required deflazacort for less than one year, and 20 for less than two years (fig 1). In these patients, the mean follow up after discontinuation of deflazacort was 9·9 months (range 1–33 months). The mean daily dose of deflazacort was 11·4 mg (range 2·5–32·2 mg) and the cumulative dose ranged between 0·9 g and 27 g (mean 6·6 g).

Twenty three of 38 patients (60·5%) had no exacerbations; 13 patients had one exacerbation,

1 had two and 1 had four. Except for two cases of frank temporal arteritis, exacerbations were mild. All exacerbations could be controlled by a temporary increase of deflazacort. No relapses were seen in 21/23 (91·3%) patients. Only two patients had relapse two months after discontinuing deflazacort.

CLINICAL EFFICACY

The visual analogue scale of pain ($F = 20·9$, $p < 0·00001$) and the duration of morning stiffness ($F = 42·3$, $p < 0·00001$) decreased at one month of follow up and on the subsequent control visits (fig 2).

LABORATORY DATA ON TREATMENT EFFICACY

ESR was raised in all patients (mean 72·9 mm/hour, range 40–114 mm/hour) on the baseline values. After one month, the mean ESR value was 30·6 mm/hour ($t = 10·95$, $p < 0·00001$). In the following months, ESR further decreased ($F = 32·58$, $p < 0·00001$) (fig 2). CRP ($F = 8·4$, $p < 0·00001$) and alpha-2-globulins ($F = 6·8$, $p = 0·00001$) also decreased; haemoglobin increased ($F = 5·3$, $p = 0·0002$).

CLINICAL TOLERABILITY

No significant changes in mean blood pressure took place during treatment. Hypertension (25 mm/Hg over baseline values) was observed in five patients who were not taking NSAIDs; in three, hypertension was present on the first visit. It was controlled by antihypertensive therapy.

The average body weight reported by the 40 patients before the onset of PMR was 68 kg (range 43·5–114·5 kg). It was 66·1 kg ($t = 3·83$, $p < 0·0004$) at the first visit. During treatment, weight increased ($F = 1·43$, $p = 0·1956$) but did not reach pre-disease levels.

LABORATORY DATA ON DRUG TOLERABILITY

The mean white blood cell count, the mean lymphocyte count, as well as the mean serum total protein concentration, transaminases, urea, creatinine, sodium and potassium remained unchanged throughout the study.

The mean platelet count (339×10^9/L at baseline) decreased significantly during follow up ($F = 2·42$, $p = 0·041$). However, all values remained within normal range.

The mean serum fasting glucose was normal throughout the study, despite a significant decrease seen on the six month control visit (5·28 *v* 4·97 mmol/L, $t = 2·26$, $p = 0·032$).

SIDE EFFECTS

Thirty six side effects occurred in 22/38 (57·9%) patients (table). These were present in 17/23 (73·9%) women and in 5/15 (33·3%) men (chi-square = 4·58, $p = 0·032$).

There was no significant difference in age, initial deflazacort dose, mean daily deflazacort dose, concomitant use of NSAIDs, and number of exacerbations or relapses between patients with adverse effects and those without. In the first group, treatment was longer [mean (SD) 21·9 (11·4) *v* 14·7 (4·7) months, $t = 2·39$, $p = 0·022$] and the mean (SD) cumulative dose higher [7910 (5716) gm *v* 4708 (2226) gm, $t = 2·12$, $p = 0·041$].

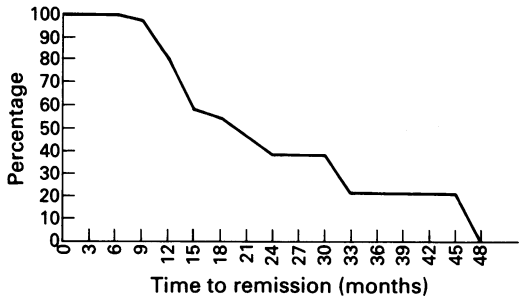

Figure 1 Kaplan-Meier survival curve showing the time of cessation of treatment because of onset of remission (used as end point) in the study population.

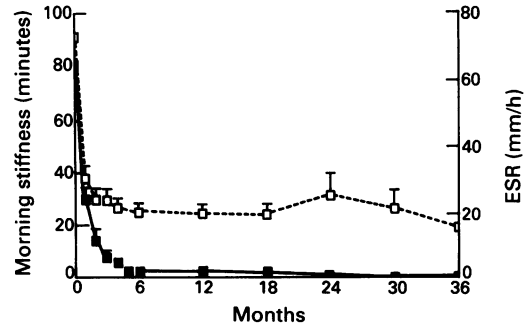

Figure 2 Changes (+SEM) in the mean duration of morning stiffness (solid squares; solid line) and in mean ESR (open squares; dashed line) during deflazacort treatment of patients with polymyalgia rheumatica. Differences from baseline values of morning stiffness were highly significant in month 2–24 ($p < 0·00001$) and for months 1 and 30–36 ($p < 0·0001$). Differences from baseline values of ESR were highly significant on months 1 through 18 ($p < 0·00001$) and for months 30 and 36 ($p < 0·001$).

Discussion

The efficacy and tolerability of deflazacort has not been tested on a long term basis in patients with PMR. In a recent double-blind study comparing deflazacort with prednisone in

Side effects of deflazacort treatment in patients with polymyalgia rheumatica

Side effect	*Number of patients*	*Mean interval* (months)*	*Mean cumulative dose (mg)*
Weight gain	7	8·6	4479
Cystitis	7	12·9	5532
Hypertension	5	10·6	6248
Dyspepsia	4	3·0	1445
Tachycardia	3	15·3	7050
Fracture	2	5·0	3982
Diarrhoea	2	6·5	2126
Exacerbation of cataract	2	17·5	4342
Exacerbation of diabetes	1	15·0	14850
Nausea	1	1·0	90
Vertigo	1	8·0	4815
Herpes zoster	1	33·0	9540

Of the 22 patients who experienced a side effect, 11 had one side effect and the other 11 had two or more side effects. *Time between beginning of treatment and the occurrence of a given side effect.

chronic inflammatory disorders, two patients with PMR have been treated with deflazacort for three months with a good response.[2] In another short term trial,[7] Lund *et al* tested patients with PMR for the relative anti-inflammatory potency of deflazacort versus prednisone. These authors concluded that the potency of deflazacort expressed on a weight for weight basis was less than that of prednisone. The median dose of 15 mg of deflazacort we used is equivalent to a value of 8·3 mg to 12·5 mg of prednisone on an equimolar basis.[7] This relatively low dose of deflazacort reduced both symptoms and objective parameters of disease activity in PMR.

We found a recurrence rate of polymyalgic symptoms of 39·5%. It is lower than the reported values of 56%[8] and 108·5%[9] with other steroids but similar to the 37·5% value of Kyle and Hazleman.[10] Accordingly, also the relapse rate of 8·3% is lower than the reported values of 35·8%,[11] 35·1%,[8] and 25·7%.[9] Under reporting of late relapses may have occurred in our study because the follow up after deflazacort withdrawal was only 9·9 months on average. However, one year after completion of the study, none of the patients returned to the clinic because of a relapse.

In our patients, median treatment was 20 months. With different corticosteroids it was 37·3 months[8] and 25·7 months.[12] These observations suggest that deflazacort has an anti-inflammatory effect that is at least comparable to that of prednisone.

The number of patients who experienced at least one side effect was 22/38 (57·9%), compared with a reported prevalence of 68·1%[9] or another of 81%[10] with prednisolone. The latter study is the only prospective study on side effects of steroids in PMR. Two other studies report side effect prevalences of 7·5%[12] and 22·6%.[8] Their retrospective design, however, may have biased interpretation of results because data were obtained from patients' records.

In all patients, body weight increased significantly after six and 12 months of treatment. However, if weight loss is considered a constitutional sign associated with untreated PMR, the mean weight did not exceed the pre-disease values reported by the patients.

The prevalence of bone fractures was lower (5·2%) than that of 13·5% observed in the UK,[13] but comparable to those of 5·8%[1] and 4%[8] in the USA. Vertebral fractures occurred after five months of treatment in two patients. Both patients reported bone fractures even before treatment with deflazacort.

Of the two patients with type II diabetes mellitus, one showed progression of the disease during treatment (fasting blood glucose previously normal on diet alone that increased to 8·6 mmol/L). Diabetes was controlled by oral hypoglycaemic agents. New cases of diabetes mellitus were not observed during the study. Mean fasting blood glucose in the remaining patients decreased slightly on the six month control. This observation may be due to the patients' paying more attention to their diet after being informed about the risks of corticosteroid therapy.

In conclusion, deflazacort has anti-inflammatory effects that are at least equivalent to those of prednisone in patients with PMR. Although no long term comparison with prednisone was performed, we propose that deflazacort is better tolerated. These considerations indicate the need for a controlled comparative trial. PMR constitutes a good model for this type of comparison because this disease has a typical, prompt response to corticosteroids and requires long term but usually definite treatment.

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